Environmental Research

Climate change and neurodegenerative diseases

--Manuscript Draft--

Manuscript Number:	ER-21-1567
Article Type:	Review article
Section/Category:	Environmental Health & Risk Assessment
Keywords:	climate change; and health; global warming; neuroinflammation; neurodegeneration; oxidative stress; excitoxicity
Corresponding Author:	Renata Del Carratore Istituto di Fisiologia Clinica Consiglio Nazionale delle Ricerche ITALY
First Author:	Renata Del Carratore
Order of Authors:	Renata Del Carratore
Abstract:	The climate change induced global warming, and in particular the increased frequency and intensity of heat waves, have been linked to health problems. Among them, scientific works have been reporting an increased incidence of neurological diseases, encompassing also neurodegenerative ones, such as Dementia of Alzheimer's type, Parkinson's Disease, and Motor Neuron Diseases. Although the increase in prevalence of neurodegenerative diseases is well documented by literature reports, the link between global warming and the enhanced prevalence of such diseases still remains elusive. This is the main theme of our work, which aims to examine the connection between high temperature exposure and neurodegenerative diseases. Firstly, we evaluate the influence of high temperatures exposure on the pathophysiology of these disorders. Secondly, we discuss its effects on the thermoregulation, already compromised in affected patients, and its interference with processes of excitotoxicity, oxidative stress and neuroinflammation - all of them related with neurodegeneration. Finally, we investigate chronic versus acute stressors on body warming, and put forward a possible interpretation of the beneficial or detrimental effects on the brain, which is responsible for the incidence or progression of neurological disorders.
Suggested Reviewers:	Tom Hopson, Dr. hopson@ucar.edu He has been working on the prediction of extreme weather events and on the link between weather and health, in particular meningitis. He is one of the few experts on weather and climate who has been working with health experts.
	Patrick Hof, Prof. patrick.hof@mssm.edu Extensive expertise in the quantitative approach to the study of selective neural vulnerability in dementing illnesses and brain evolution. NIcahn School of Medicine at Mount Sinai ash Family
	Francesca di Giuseppe, Dr. francesca.digiuseppe@ecmwf.int She has been working on the prediction of extreme heat conditions and droughts, and on how weather forecasts could be used to predict malaria outbreaks. She is one of the few experts in climate who has been working with health experts.
	Gianvito Martino Prof. martino.gianvito@unisr.it He is a leading expert in neuroinflammation
	Andrea Malaspina, Prof.

	a.malaspina@qmul.ac.uk He is an outstanding expert in cytokines within the nervous system.
	Robert Miller, Prof. millerrx@sutterhelth.org : He is a well-known neurologist expert in ALS/MND. millerrx@cpmcri.org
	Goran Simic, Prof. gsimic@hiim.hr Extensive expertise in the neuropathology of developmental and neurodegenerative disorders including biomarkers for brain diseases, especially Alzheimer's disease.

Dear Prof. Domingo,

We would be pleased to present our Review “Climate change and neurodegenerative diseases” for publication on “Environmental Research”.

All of the Authors have read and approved the paper and it has not been published previously nor is it being considered by any other peer-reviewed journal.

Hoping you will find it suitable for publication,

Yours sincerely.

Renata Del Carratore

Climate change and neurodegenerative diseases.

Paolo Bongioanni[a,b], Renata Del Carratore*[c], Silvia Corbianco[d,e], Andrea Diana[f], Gabriella Cavallini[d], Silvia M. Masciandaro[b,c], Marco Dini[d,e], Roberto Buizza[g]

[a] Severe Acquired Brain Injuries Dpt Section, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[b] NeuroCare onlus, Pisa, Italy
[c] Institute of Clinical Physiology, National Research Council, Pisa, Italy
[d] Interdepartmental Research Centre on Biology and Pathology of Aging, University of Pisa, Italy
[e] Human Movement and Rehabilitation Research Laboratory, Pisa, Italy
[f] Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy
[g] Scuola Superiore Sant'Anna and Centre for Climate Change studies and Sustainable Actions (3CSA), Pisa, Italy

*Corresponding author: Renata Del Carratore
Institute of Clinical Physiology, National Research Council, Pisa, Italy
e-mail: rdc@ifc.cnr.it
telephone +39 050 3152778 mobile:347 6644425

Abstract

The climate change induced global warming, and in particular the increased frequency and intensity of heat waves, have been linked to health problems. Among them, scientific works have been reporting an increased incidence of neurological diseases, encompassing also neurodegenerative ones, such as Dementia of Alzheimer's type, Parkinson's Disease, and Motor Neuron Diseases.
Although the increase in prevalence of neurodegenerative diseases is well documented by literature reports, the link between global warming and the enhanced prevalence of such diseases still remains elusive. This is the main theme of our work, which aims to examine the connection between high temperature exposure and neurodegenerative diseases. Firstly, we evaluate the influence of high temperatures exposure on the pathophysiology of these disorders. Secondly, we discuss its effects on the thermoregulation, already compromised in affected patients, and its interference with processes of excitotoxicity, oxidative stress and neuroinflammation - all of them related with neurodegeneration. Finally, we investigate chronic versus acute stressors on body warming, and put forward a possible interpretation of the beneficial or detrimental effects on the brain, which is responsible for the incidence or progression of neurological disorders.

Key words: climate change and health, global warming; neuroinflammation; neurodegeneration; oxidative stress; excitoxicity

Authors declare that there was not any funding source.

Declaration of competing interest:
The Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1 Clinical impacts of exposures to high temperature linked to climate change

The Earth climate is warming, sea-ice and glaciers are melting quickly, and sea-level is rising fast (IPCC, 2019). Strong evidence of this warming comes for 2020, which was the warmest year on record since 1979 in terms of average global temperature (a-par with 2016), and the warmest ever for Europe (WMO, 2021). Considering Europe, 2020 follows 2019, the second warmest year on record, and 12 of the 13 warmest years have occurred since 2000 (C3S, 2020). In terms of global average surface temperature, with respect to the pre-industrial value, in 2020 the Earth global mean temperature was about 1.3°C warmer, with an accelerating warming trend which stands at about 0.2°C per decade. Although the warming is a global phenomenon, its intensity has not been spatially uniform: for example, nowadays the European average surface warming is about 2°C, and the average warming of the countries facing the Mediterranean Sea is about 3°C (IPCC, 2014; IPCC, 2018; IPCC, 2019), compared to the 1.3°C increase of the global average temperature. This average warming is associated also with more frequent and more intense heat waves (Table 1), especially during the summer months, increased evaporation and reduced soil moisture, which lead to more frequent and longer drought episodes with a clear impact on agriculture and farming.

Increased temperatures and especially more frequent, prolonged and intense heat waves, affect human and animal health. During the August 2003 European heat wave, one of the hottest August on record for many countries (Schaer and Jendritzky, 2004), for example, there have been reports of more than 20,000 deaths: ~15,000 people died in France, ~ 2,000 in the UK, ~ 2,100 in Portugal, ~3,100 in Italy, ~ 1,500 in Holland and ~ 300 in Germany (UKMO, 2003). Rivers (e.g. the Danube, the Seine) fell to their lowest levels, causing disruption in electricity production, thus making it difficult for some areas to have access to enough electricity to be able to cool down buildings. Forest fires broke down in many countries (e.g. in Portugal, more than 200,000 hectares were destroyed). As for other extreme events, the link between heat waves and man-induced climate change was studied for the 2003 event: Stott et al. (2004) concluded that, at a confidence level of greater than 90%, more than half of the risk of 2003-like extreme European summers is attributable to human influences on the climate system.

Climate projections indicate that, if we continue to emit greenhouse gases as we have done in the past decades, the world will warm even further the limit of the 1.5°C warming that countries pledged not to surpass at the United Nations Conference of the Parties of 2015 in Paris (IPCC, 2018; COP21, 2015). As a consequence, future generations will be facing even more critical

situations than those that we have been witnessing in the last years: the European heatwaves of 2003 (Della Marta et al., 2007), the Australian fires of the end of 2019 and the beginning of 2020, the US west-coast fires on summer 2020, the extreme water levels in Venice of 2019, extreme storms like the tempest Vaia that hit the Dolomites in 2018, drought and landslides that annually affect many countries. Global average warmings are projected to reach about 2.5°C if emissions continue to rise at the current level, following the projections represented by the IPCC Representative Concentration Pathway 6.0 (RCP6.0). As the warming continues, glaciers will be melting and the sea-ice will continue to rise. Unfortunately, recent reports of the status of the Arctic (in October and November 2020, the sea-ice extent reached the lowest extension for those months, and in September 2020 was very close to the minimum observed in 2012) and the Greenland ice-sheet suggest that the warming is accelerating.

In the past decade, an increasing number of studies have been investigating the health effects of the exposure to high temperatures, or to sudden large temperature changes, especially among older populations (Zanobetti et al., 2012; Shi et al., 2015; Shi et al., 2016; Andrews et al., 2018). They have reported that the health impact of prolonged heat exposure includes heat stress, heat exhaustion, heat stroke, hyperthermia and multiorgan-dysfunction syndrome (Table 1). A World Health Organization (WHO, 2020) assessment concluded that climate change is expected to cause approximately 250,000 additional deaths per year between 2030 and 2050; 38,000 due to heat exposure in elderly people. Prolonged exposure to heat might also result in additional diseases and death, by exacerbating pre-existing chronic conditions such as various cardiovascular (Gostimirovic et al., 2020) and neurological diseases (Gulcebi et al., 2021). It can also increase the risk for patients taking psychotropic drug treatment for mental disorders, due to the body's impaired ability to regulate temperature (Chesire, 2016).

Neurological disorders are increasingly recognised worldwide as major causes of death and disability. Globally, neurological disorders were, after cardiovascular diseases, the second cause of death and the main cause of disability-adjusted life-years (DALYs) in 2016: around 280 million patients in the world with a fatal outcome for 9 million of them (Feigin et al., 2019). The absolute number of deaths and DALYs from all neurological disorders combined increased between 1990 and 2016, and the burden of neurological disorders continues to increase.

An improved understanding of altered pathways and biomarkers during global warming exposure will contribute to the identification of effective prevention and control measures in patients with neurological diseases, and particularly with neurodegenerative diseases, where a likely genetic predisposition to abiotrophy can be associated with an acquired damage resulting from chronic exposure to heat (Peinkhofer, et al., 2020). Unfortunately, how heat exposure can directly modulate

human neuronal pathways is still far to be understood. Therefore, the need to acquire better understanding on biomedical alterations and diseases linked to climate change, and in particular global warming, is becoming extremely important.

In this review, we describe clinical features, the epidemiology and the neuropathology of the main neurodegenerative disorders and hints on altered thermoregulation. Moreover, we review the main results reported in recent literature on the effects of heat influences on neurodegenerative diseases' pathophysiological mechanisms. The relevance of the heat stress toward the main processes of excitotoxicity, oxidative stress and neuroinflammation will also be discussed.

2 Neurodegenerative disorders

2.1 Dementia of Alzheimer's type

Dementia of Alzheimer's type (DAT) is known to be the most predominant cause of dementia among the aged people associated with subsequent behavioral disturbances, and clinically characterized by cognitive impairment and the limitation of daily activities (Scheltens et al., 2016).

The number of DAT patients was 20.2 million in 1990, whereas it reached 43.8 million in 2016: an increase of approximately 120%, contrasted only by a slight increase in age-standardised prevalence of about 2% (Nichols et al., 2019). In 2016, DAT was globally the 5th leading cause of death, with 2.4 million deaths: overall, around 30 million DALYs were attributed to DAT.

DAT, as well as Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Diseases (MND), are neuropathologically characterized by protein misfolding and aggregation into cells or into extracellular deposits - hallmarks of neurodegenerative disorders (Lim, 2019; Medinas et al., 2019). Newly synthesized proteins must be folded to form their proper three-dimensional structures. Several types of stress elicit perturbation to protein folding, thereby leading to the overwhelming precipitation of misfolded or aggregated proteins. The aggregation can be a random event implying protein hyperphosphorylation, resulting from the following pathways: prion self-catalytic conformational conversion, mutations altering the protein stability, and uncontrolled pathological increase in the intracellular content of these selected proteins. Such imbalances in protein concentration can be a consequence of mutations such as duplications of the amyloidogenic gene or changes in the protein's amino acid sequence. Imbalances can be caused also by deficiencies in the proteasome, the cellular machinery involved in the degradation of aging proteins (Sweeney, et al., 2017).

Neuropathologically, DAT is characterised by the presence of extracellular amyloid plaques containing amyloid β (Aβ) peptide, and intracellular neurofibrillary tangles (NFTs) composed of

hyperphosphorylated Tau protein. The Aβ peptides responsible for plaques formation are derived by the cleavage of Aβ precursor protein produced by the amyloidogenic pathway, and the main mutations related with the disease dramatically dictate the proteolytic processing by β- and γ-secretases (Lim, 2019; Webers et al., 2020): several studies indicate that the presence of Aβ could be a consequence of molecular events in the DAT cascade rather than the cause of neurodegeneration itself (Mecocci, 2018). Tau is a microtubule-binding protein abundant into the central nervous system (CNS) and when hyperphosphorylated is converted into the pathological form that is aggregated into insoluble NFTs (Webers et al., 2020).

DAT patients have been found to have significant circadian dysfunction in core body temperature, which may precede clinical onset. Since disease severity might be related to the extent of circadian dysfunction (Coogan et al., 2013; Knight el al., 2013), dementia bearing people would be reasonably more affected by the phenomenon of global warming. A metabolic hypothesis has suggested that there is a significant correlation between risk factors, including body temperature, and DAT onset (Whittington et al., 2010). Several findings put forward the hypothesis of a correlation between age-related alteration in temperature homeostasis and dysregulation of Tau phosphorylation in DAT (Whittington et al., 2010; Carrettiero et al., 2015; Keil et al., 2015).

2.2 Parkinson's Disease

PD is a chronic and progressive neurodegenerative disorder. Tremor, bradykinesia-akinesia and rigidity, depression and other non-motor symptoms, as well as cognitive dysfunctions, often occur in the course of PD.

In 2016, more than 6 million subjects were affected by PD globally, while they were only 2.5 million in 1990 (Dorsey et al., 2018). PD caused about 212,000 deaths and more than 3·million DALYs in 2016. Nowadays the global PD burden has more than doubled, when compared with the past century, due to an increase in the number of elderly people, with potential contributions from longer disease duration and environmental factors. Demographic and other factors are expected to determine a dramatic increase in the future PD burden (Dorsey et al., 2018).

Misfolded forms of alpha-synuclein (α-syn) represent the PD neuropathological hallmark and are associated with the formation of Lewy Bodies (LBs) into *substantia nigra* neurons (Kim et al., 2014; Power et al., 2017). Different models were proposed to explain the formation of α-syn aggregates in PD (Liu et al., 2012$_b$, Kim et al., 2014). Increased "normal" α-syn itself associated with post-translational modifications as phosphorylation may lead to toxicity. Moreover, a plethora of α-syn genes supports α-syn overproduction followed by aggregation. The failure of protein quality control systems, such as ubiquitin-proteasome system or lysosomal degradation (e.g.,

autophagy-lysosomal pathway), promotes the endoplasmic reticulum (ER) stress with consequent accumulation of misfolded proteins that may form toxic proteins, like α-syn oligomers (Valdinocci et al., 2017).

PD patients may exhibit a spectrum of thermoregulatory symptoms, which can be exacerbated by heat stress and heat waves. Thermoregulatory dysfunction in PD patients has been observed mainly as excessive sweating and vasomotor abnormalities such as episodes of intermittent hyperhidrosis, night sweats or hypohidrosis, which are secondary consequences due to neurodegeneration processes (Coon, E.A., et al.,. 2020). Pathological involvement of the hypothalamus due to the formation of LBs has been reported in PD patients (Orimo et al., 2008). Furthermore, α-syn-containing LBs were found in the medulla, co-localized with tyrosine hydroxylase, thus highlighting the involvement of sympathetic nuclei (Kingsbury et al., 2010). Indeed, in PD, apart from the LB formation, small- and large-fiber peripheral neuropathies represent a common complication (Doppler et al., 2014). In the early stages of the disease small-fiber neuropathies can be associated with impaired thermoregulation, as autonomic innervation of blood vessels, sweat glands, and erector pili muscles is reduced (Podgorny et al., 2016). Beside the fact that α-syn accumulation in sympathetic ganglia is associated with central thermoregulatory alteration in PD, l-dopa treatment might be a potential cause of neuropathy that is observed in late-onset disease and is relevant in patients exposed to l-dopa (Ceravolo et al., 2013).

An interpretative model for thermal regulation in PD patients brains has been proposed by Chen et al (2020) and is based on mitochondrial dysfunction as neuroinflammatory trigger for oxidative stress, thus resulting in cell death, lower metabolism and lower intraventricular temperature.

2.3 Amyotrophic Lateral Sclerosis/Motor Neuron Diseases

MNDs, leading to progressive muscle weakness and atrophy, are a group of neurodegenerative disorders, which include ALS, primary lateral sclerosis, hereditary spastic paraplegia, pseudobulbar palsy, spinal muscular atrophy and progressive muscular atrophy. MNDs lead to progressive muscle weakness and atrophy related to upper and lower motor neuron involvement. Namely, they are related with the degeneration of pyramidal neurons in the motor cortex, cranial motor neurons and anterior horn cells in the spinal cord. In 2016, globally, about 331,000 subjects have received a MND diagnosis: there were more than 925,000 DALYs and almost 35,000 deaths. The worldwide prevalence for all ages was 4.5 per 100,000 people, with an age-standardised prevalence increase of 4.5%; the all-age incidence was 0.78 per 100,000 person-years (Logroscino et al., 2018). In ALS/MND protein misfolding has been included among the pathogenic factors responsible for neuronal death. The main mutations were observed in superoxide dismutase (SOD)1 gene, and

SOD1 aggregates were localized into the ER, giving rise to protein aggregate overexpression and activating the unfolded protein response (UPR) to restore ER proteostasis (Medinas et al., 2019). Interestingly, ALS/MND induced pluripotent stem cell-derived motor neurons carrying mutations in SOD1 displayed an increase in insoluble proteins, as the SOD1 (Seminary et al., 2018).

Concerning with temperature dependent variables, the well-known ALS/MND hypermetabolic state may contribute to thermoregulatory defects: intrinsic metabolic abnormalities in skeletal muscle represent a possible cause of energy dissipation, and might compromise the thermoregulatory balance (Bouteloup et al., 2009). It is interesting to report that on the Island of Guam some people are affected by an endemic ALS form intermingled with other motor syndromes (the so-called Guamanian ALS). It was discovered an altered variant of the heat receptor (transient receptor potential cation channel, subfamily M (melastatin), member 2 -TRPM2), implicated in central heat sensation (Hermosura et al., 2008). The relevance of TRPM2 or other central thermoreceptors has not been further substantiated since the discovery reported above (Song et al., 2016).

Despite the current lack of information on the involvement of thermoregulatory hypothalamic centers in ALS/MND patients, a 15% reduction in hypothalamic volume in a magnetic resonance imaging study of 270 patients, compared to age- and sex-matched controls, was observed (Gorges et al., 2017). Altered melanocortin pathway is consistent with the metabolic abnormalities present in ALS/MND patients (Huisman et al., 2015) and in animal models (Dupuis et al., 2004). In the hypothalamus of the human SOD1 mutated transgenic mouse (an animal model for ALS/MND), an impaired melanocortin tone was correlated to the increased agouti-related protein levels in the arcuate nucleus (Vercruysse et al., 2016).

Deranged raphe pallidus serotonergic receptors might also participate to the altered thermoregulatory defect in ALS/MND patients: brainstem serotonergic neurons degenerate in patients as well as in animal models (Dentel et al., 2013), promoting muscle hypertonia (El Oussini et al., 2017). Remarkably, peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) has been linked to defective thermoregulation via its muscle-specific effects: polymorphisms in the PGC-1α encoding gene are associated with age at onset and survival of male ALS/MND patients (Eschbach et al., 2013), as well as with patients' response to exercise (Pasquinelli et al., 2016). Anyway, further work is needed to determine the exact role of PGC-1α to abnormal energy metabolism and defective thermoregulation during disease progression.

3 General heat effects on neuronal system

Heat stress has multiple effects on living organisms. Despite specific studies are still limited, it is emerging the concept that prolonged exposure to high temperatures is the common element for diverse pathophysiological changes, including neuronal damage (Lee et al., 2015; Chauhan et al., 2017). Heat stress prompted hyperthermia, once considered as non-toxic in the mammalian nervous system, produces specific modifications in the CNS that may have long-term neuropathological, functional and behavioural consequences. Because of the recent consideration of heat stress impact on neuronal cell degeneration, chronic heat stress due to global warming might be critical for the development of neurodegenerative disorders (Habibi and Perry, 2014; O'Donnell, 2018).

Since the CNS is the interaction hub of a living body with the environmental domain, the neurobiological implications of climate change are paramount features for the comprehension of human adaption to the increasing temperature trend. Indeed, it emerges that on animal models climate warming can alter gene expression, neuronal structure and brain organization (Amiel et al., 2017; Pallotta et al., 2017). Structural changes due to exposure of rats to heat (37-40 °C) have been observed in neurons and their axons, in the glia and in the cerebral vascular endothelium (Sharma and Hoopes, 2009). Heat stress compromises the blood-brain barrier with an increase in its permeability and development of cerebral edema in rats (Sharma et al., 2010). In mice with mild traumatic brain injury, exposed to hyperthermia, long-term memory and learning deficits are observed (Titus et al., 2015). Moreover, climate warming affects animal learning ability (Dayananda and Webb, 2017). In humans, environmental hyperthermia (50°C) has been shown to impair functional connectivity of the brain, with alterations in cognitive and work performance (Sun et al., 2013), as well as in short-term visual memory (Jiang et al., 2013). Ten studies investigated the effects of high environmental temperatures on demented patients (Wei, 2019; Peinkhofer et al., 2020): in 8 of them enhanced temperatures were associated with worsening of symptoms (including agitation) and increased rates of hospitalization and mortality. Two studies evaluated the effects of high temperatures on PD patients (Zanobetti et al., 2013; Linares, 2016). Although the former in a large number of PD patients in extremely hot days (maximum temperature of 31,7°C) found no association between mortality and environmental temperatures (Zanobetti et al., 2013), the latter indicated a correlation between high environmental temperature (>34°C) and an increase risk of excess morbidity and mortality in PD patients (Linares, 2016). All those findings highlight how heat waves may worsen neurological symptoms or be considered as risk factor that, to some extent, contributes to the boost in both morbidity and mortality associated with high temperatures. Moreover, it is well established that with advancing age and facing longer lasting life expectation,

body temperature physiologically decreases (Lu et al., 2010; Waalen and Buxbaum, 2011) and becomes progressively more variable, as a probable result of thermoregulatory failure (Tan et al.,2020; Cheshire, 2016). Therefore, the response to heat is further worsened and likely promote a vicious circle in the progression of neuronal impairment and demise. Brain temperature is regulated by various factors, such as metabolism, body temperature, blood flow, and by heat shock proteins (HSP), important molecular components which are activated when the temperature rises. In humans, for whom aging is also associated with cerebral hypometabolism that promotes cognitive impairment (Cunnane et al., 2011) heat might induce a brain temperature derangement associated with a significant reduction in neuron basal metabolism (Kiyatkin, 2019). In neurodegenerative disorders, brain temperature might be affected by enhanced oxidative stress and neuroinflammatory processes, which can significantly interfere with it (Iodice et al., 2011; Rango et al., 2014). Relevant information might derive from the study of how molecular components, such as HSP or misfolded proteins, and neurodegeneration mechanisms, such as **excitotoxicity, oxidative stress and neuroinflammation** are influenced by environmental temperature (Fig.1).

4 Pathogenetic pathways and biomarkers related to global warming/heat stress effects.

4.1 Heat stress and misfolded proteins

Different types of stress, including heat stress, may cause protein misfolding, thereby producing enhanced amounts of aggregated proteins, which are then degraded through proteasomal and lysosomal pathways (Vabulas et al., 2010). In animal models, hyperthermia could cause a molecular phenotype similar to DAT with upregulation of Aβ expression and phosphorylated Tau deposition (Sinigaglia-Coimbra et al., 2002). It has also been shown that slight variations in temperature might considerably change the folding of Aβ and accelerate the aggregation process (Ghavami et al., 2013). Nevertheless, some studies indicate that induced-hypothermia (such as after anesthesia) is associated with a significant increase of hyperphosphorylated Tau (Planel et al., 2004) contained in the intracellular NFTs, and higher values of ambient temperature have been suggested in helping mitigate dementia symptoms by reducing the production of Aβ peptides (Vandal et al., 2016).

Up to date, still inconsistent and poorly understood results are reported on the effects of temperature on phosphorylated Tau (Carrettiero et al., 2015) leading to the conclusion that these proteins might have heat sensitive properties. In addition, misfolded protein accumulation and aggregates formation in neurodegenerative diseases (DAT, PD and ALS/MND) upregulate pro-inflammatory molecules (Stephenson et al., 2018).

4.2 Heat shock proteins

HSPs have evolved to protect the organisms from thermal stress (Singh et al., 2013; Miller and Fort, 2018). They play a crucial role in the folding of nascent chain peptides, in the translocation of proteins across the membrane and in their protection from the effects of high temperature (Katschinski et al., 2004). Some HSPs are located on the membrane of extracellular vesicles released from macrophages after heat stress (Fukuoka et al., 2014). During cell exposure to warming, HSP are immediately activated to function as molecular chaperons for restoring the normal fold of heat-denatured proteins (Miller and Fort, 2018). HSPs help in protecting neurons from the aggregation of toxic misfolded proteins: therefore, their malfunction or exhaustion might contribute to the pathogenesis of neurodegenerative disorders (Malyshev, 2013).

The cellular reaction to heat stress and protein misfolded activates the UPR that triggers to ER sensory proteins and the mitochondrial unfolded protein response pathway that, in turn, up-regulates HSPs, such as HSP-10, HSP-60 and HSP-70 (Homma et al., 2016; Ji et al., 2020; Salminen et al., 2020). Exposure of cortical neurons to heat causes ER stress, inhibiting protective feedback to heat shock (Liu et al., 2012$_a$) and enabling autophagy to take place (Kabir et al., 2018). Therefore, an UPR dysregulation causes a lack of induction of autophagy which fails to eradicate the accumulation of "contagious" proteins (such as Aβ) and then consequently leads to neurodegenerative diseases (Kabir et al., 2018).

Nevertheless, accumulating evidence indicates that autophagy operates as a double-edged sword, with appropriate activation of the autophagic pathway playing a cytoprotective role under pathological conditions, but overstimulation or suppression of autophagy results in amplification of pathological lesions via the induction of autophagy-dependent programmed cell death. An increasing number of studies shows that the dysregulation of autophagy is closely linked with the occurrence and progression of neurodegenerative diseases (Yan and Xu, 2020).

A distinctive feature of heat-induced mitochondrial dysfunction, the irreversible mitochondrial membrane potential depolarization, with subsequent lacking of HSP production, causes misfolded protein accumulation and apoptotic signaling activation. This evidence has been proposed as the potential mechanism of hyperthermia-induced death of cultured rat neurons (White et al., 2012).

In DAT patients, Aβ and Tau accumulation and deposition are associated with impairment or loss of function in the HSP-60, direct consequence of the oxidative and/or heat stress (Campanella et al., 2018). The upregulation of UPR phosphorylated markers was detected in DAT patients' neurons, thus demonstrating a higher level of heat shock response (HSR) activation (Salminen et al., 2020).

Alpha-syn overexpressing neuronal cells exposed to heat stress (50°C) did not display aggregate assembly, as α-syn remained in the monomeric form (Fragniere et al., 2019). However, the role of

HSP and the HSR is crucial for a correct response to α-syn aggregates since HSP-70 is able to induce α-syn degradation through the HSP-mediated autophagy-lysosomal pathway (Jones et al., 2014). As far as MND is concerned, SOD1 cells exposed to heat stress (42°C for one hour) exhibited transcript levels of HSP-B1 and HSP-B8 and phosphorylated heat shock factor-1 (HSF-1) protein levels significantly higher compared with the unstressed state. This suggests the crucial role of the heat stress in the modulation of the protective HSR (Qu et al., 2018).

5 Heat-modulated excitotoxicity, oxidative stress and neuroinflammation

5.1 Excitotoxicity

Excitotoxicity is a complex process triggered by an excess in excitatory amino acid (e.g., glutamate and aspartate) receptor activation. This process provokes a certain number of deleterious consequences, including impairment of calcium buffering, generation of free radicals, activation of the mitochondrial permeability transition pore, dendrites degeneration, and ultimately cell death. All the subcellular compartments are affected by the excitotoxic process, with changes in the cytosol, mitochondria, ER, and nucleus being pivotal. Excitotoxicity can damage neurons upon metabolic and oxidative stress conditions, which occur after a stroke episode, a traumatic brain injury or in age-related neurodegenerative disorders, and seems to play a significant role in heat-induced brain damage (Ruszkiewicz et al., 2019). In rats, heat stress (38°C) significantly intensified the levels of brain excitotoxic neurotransmitters glutamate and aspartate, whereas concentrations of inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine were reduced, with a shift to excitatory neurotransmitters causing enhanced neurodegeneration (Sharma, 2006). Such findings are related with decreased hippocampal GABAergic synaptic transmission (Qu et al., 2007). Systemic glutamate levels were downregulated in rats exposed to mild hyperthermia (37-39 °C), whereas further heating (42 °C) significantly elevated circulating glutamate concentrations (Zlotnik et al., 2010). Moreover, glutamatergic down-regulation resulted in a protective effect in acclimation (Ely et al., 2015). Hyperthermia was shown to cause depolarization together with increased synaptic activity of hippocampal pyramidal cells, being also indicative of higher brain excitability (Kim and Connors, 2012). Furthermore, the resulting impaired Ca^{++} homeostasis at synaptic level may also add its contribution to neuronal damage under heat exposure (White et al., 2012). Hyperthermic-dependent Ca^{++} dysregulation has also been found in pathogenetic mechanisms of other systems, like endothelial cells (Li et al., 2015), which may exert the function in impaired cerebrovascular reactivity at heat stress exposure (Ruszkiewicz et al., 2019).

5.2 Oxidative stress

Neuronal oxidative stress identifies a serial of biochemical processes with possible dramatic consequensces on cerebral metabolism. Oxidative stress occurs upon excessive free radical production resulting from an insufficient antioxidant response system. Such an imbalance between antioxidant activity and reactive oxygen species (ROS) production has a direct effect on the accumulation of free radicals, mitochondrial dysfunction, and neuronal injury during the progression of age-related neurodegenerative diseases, linked to cellular failure in keeping constant the redox balance (Adibhatla and Hatcher, 2010). Thus, heat stress induces mitochondrial dysfunction and oxidative stress in neurons (Akbarian et al., 2016). High temperature exposure has a relevant influence in boosting mitochondrial superoxide anion levels (Mujahid et al., 2007) and decreasing the expression and activity of the antioxidant SOD in neuronal cells with fatal outcome for neuronal structures (El-Orabi et al., 2011). Furthemore, heat stress is known to induce mitochondrial dysfunction in cultured rat central neurons, espressed by large number of mitochondrial fragments (White et al., 2012; Yu et al., 2015). That situation causes dysfunction of the mitochondrial electron transport chain (ETC) resulting in increased superoxide and further increase in ROS production (Zorov et al., 2014; Yu et al., 2015). Heat-induced ROS accumulation within mitochondria has a negative influence on the oxidation of ETC components, including lipids, proteins, and DNA, and causes mitochondrial outer membrane permeabilization with release of proapoptotic factors and irreversible activation of apoptotic signalling (Wang et al., 2013). Thus, mitochondrial dysfunction, apoptosis and oxidative stress with ER oxidation may underlie heat-induced neurodegeneration. These observations are in agreement with the occurrence of tight interplay between ER and oxidative stress in brain pathology (Thornton et al., 2017). Therefore, heat stress is interpreted as an environmental pro-oxidant factor (Slimen et al., 2014). As a matter of fact, exposure to heat (44 °C) has been shown to trigger cerebral oxidative stress and Tau pathology in laboratory rodents (Chauderlier et al., 2017; Chauhan et al., 2017), confirming the link between hyperthermia and neurodegeneration.

5.*3* *Neuroinflammation*

Exposure to high temperature deeply alters the immune system of animals (Dahl et al., 2020) acting as a physiological input for inflammatory/immune response (Suzuki et al., 2020). The immune response aims to defend an organism against foreign aggressors. The potential pathogens include living organisms such as microorganisms, viruses, bacteria, parasites, and fungi or chemico-

physical agents. Two distinct immune responses have been identified, the innate and the adaptive ones, which cooperate to protect against pathogens. The innate immune response is known to be a non-specific and quick response to any sort of pathological agents, by activation of immune cells such as neutrophils, macrophages, and monocytes, and soluble factors including cytokines. The adaptive response, provided against specific antigens, encompasses cells such as dendritic cells, T and B cells, as well as antibodies, known as immunoglobulins, which directly interact with antigens. The communication between immune and inflammatory cells is mediated in large part by a subset of cytokines known as interleukins (IL) which consist of more than 40 different proteins that can elicit many reactions in cells and tissues by binding to high-affinity cell receptors. The majority of ILs are synthesized by helper $CD4^+$ T lymphocytes, as well as by monocytes, macrophages, and endothelial cells. Cytokines play essential roles in the activation and differentiation of immune cells (such as T and B lymphocytes), as well as their proliferation, maturation, migration, and adhesion. They also have pro-inflammatory (IL-1, IL-12, tumor necrosis factor (TNFα), interferon (IFN) γ) and anti-inflammatory (IL-10, IL-15, IL- 18, and IFNβ) properties (Dantzer, 2018). Bidirectional communication between the peripheral immune system and the CNS may be a complex mechanism by which resident brain cells are stimulated to produce cytokines (mainly IL-1β, IL-6 and TNF-α). The neuroimmune system consists of glial cells (astrocytes, oligodendrocytes and microgliocytes), brain macrophages and resident/circulating lympho/monocytes collectively called "neuroimmunocytes".

The release of inflammatory molecules may play a significant role in neurological disorders (Alinejad et al., 2020) and can provide protection to CNS (e.g. removal of cell debris or secretion of neurotrophic factors), although it might implicate harmful effects, as inflammatory mediators can be recruited for the neurodegenerative pathway (Kempuraj et al., 2016; Calabrese et al., 2018).

Immediately after an acute brain injury or infection, neuroinflammation ensures the efficient immune response, eliminating cellular debris and pathogens as a precursor to permitting tissue repair and regeneration. Similarly, in chronic neurodegenerative diseases, such as protein-misfolding disorders, neuroimmune cells offer their decisive role for the elimination of toxic protein aggregates, at least in the initial phase. However, the long duration of the generating stimuli results in excessive, chronic inflammation and uncontrolled neuroimmunocyte activation finally being the key player to further assist in tissue injury and disease progression. (Dukay et al., 2019) Therefore, neuroinflammatory processes should be tightly regulated to maintain the balance between benefits and the over-activated, harmful effects of the immune cells (Dukay et al., 2019).

In neurological conditions, microglia can be activated and secrete proinflammatory cytokines and neurotoxic mediators, such as TNF-α, IL-1β, IL-6, nitric oxide and ROS, which cause additional

neuroinflammation (Gelders et al., 2018; Neal and Richardson, 2018) and negatively influence brain disease progression (Konovalova et al., 2019). Different factors, such as protein mutations, oxidative stress and impairments in the protein quality control system, can lead to aggregates formation and deposition, activating a neuroinflammatory response in DAT, PD and ALS/MND (Reish and Standaert, 2015, Michaelson et al., 2017, Webers et al., 2020).

Microglial activation in response to Aβ peptides might result in both positive and detrimental effects in DAT patients (Webers et al., 2020). The physiological role is related with the clearance of apoptotic bodies, Aβ, debris, with the secretion of neurotrophins and cytokines and the migration to damaged tissues; the pathological role is activated by the detrimental effects of cytokine secretion, the impaired Aβ clearance and the increased reactivity to NFTs (Webers et al., 2020).

Inflammatory markers in peripheral blood can affect PD progression (Chen et al., 2020). Higher levels of apoptotic leukocytes, nuclear DNA levels, and vascular cell adhesion molecule 1 levels in PD patients were associated with the involvement of systemic inflammation (Chen et al., 2020).

The association between neuroinflammatory response and ALS/MND has been investigated, demonstrating macrophages and microglia migration in the spinal cord and peripheral nerve of the transgenic rat model of ALS, as well as the innate and adaptive immune response activation and the release of IL6, IL-17, TNFα and IFNγ (Michaelson et al., 2017).

The proinflammatory response of microgliocytes that function as brain macrophages (Ginhoux et al., 2013) is activated by high temperature: the neuroinflammatory responses of microglial cells play an important role in the process of brain dysfunction caused by heat, provoking release of inflammatory cytokines and neurotoxic mediators, which exert additional neuroinflammation and aggravate brain disease progression (Beckers et al., 2018).

Prolonged heat exposure in mice resulted in a proinflammatory environment being characterized by increased of the nuclear transcription factor NF-κB signaling (Lee et al., 2015; Christoforidou et al., 2020). The NF-κB regulates multiple aspects of innate and adaptive immune functions such as inflammatory T cells; stimulates the expression of various pro-inflammatory genes, including those encoding cytokines (Liu et al., 2017). Moreover, prolonged exposure to heat upregulated the expression of IL-1β, IL-6, TNF-α, cyclooxygenase-2 and inducible nitric oxide synthase in hippocampus with subsequent decrease in neuronal and synaptic density, and gliosis (Lee et al., 2015; Christoforidou et al., 2020). High levels of circulating IL-6 showed the highest correlation with neurological symptoms and morbidity of heat stress in patients and animal models (Suzuki et al., 2020). Higher levels of cytokines in PD patients were positively correlated with higher intraventricular temperature (Chen et al., 2020): correlation with brain temperature and PD progression was studied in different age groups of PD patients (Chen et al., 2020).

Neuroinflammation was also associated in heat-stressed (42°C) animals with systemic inflammatory response (Leon and Helwig, 2010) and with dysfunction at the mitochondrial level (White et al., 2012).

Ultimately, heat exposure might cause neurodegeneration through the derangement of mitochondrial function, the impairment of the biochemical processes amending protein misfolding and the enhancement of oxidative stress, excitotoxicity and neuroinflammation, that can promote further protein misfolding and aggregation in neurons exposed to unfavourable conditions.

6 Conclusions

Climate change is real global phenomenon, and it is rapidly and extensively disrupting ecosystems worldwide. It has also been reported to have a dramatic impact on human health, although its mechanisms are still far from being completely explained. In particular, the way the human body reacts to being exposed to more frequent, longer and intense global warming is not yet completely understood, and this makes the development of effective adaptation strategies rather challenging.

In our review, we tried to underline specific pathways mediating the heat effects at cellular level. Even if high temperatures positively affect certain protective mechanisms at the CNS level, the harmful effects of an exposure to high temperature dominates, as it has been confirmed by findings that long exposure to high temperatures definitely damages the nervous system in several ways.

Thus, we would conclude that heat stress due to global warming can significantly increase the rate of neurodegenerative disorders. Such a stress might cause DNA damage, protein misfolding and aggregation, induction of apoptotic pathways and autophagy within neurons, which could further expose susceptible cells to neurodegeneration. Our hypothesis is that certain mechanisms of heat stressors stimuli might play a role in increasing the prevalence of neurodegenerative diseases and/or worsening functionality of affected patients, whose thermoregulation results compromised.

Climate change adaptation measures could include therapeutic intervention based on heat therapy and/or acclimation, which tend to upregulate HSP expression (Hunt, 2020), providing neuroprotective effects both in healthy and neurologically affected people. Indeed, the latter used to undertake moderate to frequent sauna bathing are less prone to get DAT (Laukkanen, 2017), thus opening a revolutionary scenario related with the potential benefits of passive heating for the prevention of neurodegenerative diseases. Since setting a strict clinical (not observational retrospective) study has been impossible so far, it might be conceived that the opposite effects of chronic versus acute thermic stress are played within a certain temperature and temporal threshold still to be assessed. At the moment, this remains only an alluring suggestion that should be corroborated by further scientific evidence.

References

Adibhatla, R.M., Hatcher, JF. 2010. Lipid oxidation and peroxidation in CNS health and disease: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 12, 125-169. doi: 10.1089/ars.2009.2668.

Akbarian, A., et al., 2016. Association between heat stress and oxidative stress in poultry; mitochondrial dysfunction and dietary interventions with phytochemicals. J. Anim. Sci. Biotechnol. 7, 37-50. doi: 10.1186/s40104-016-0097-5.

Alinejad, T., et al., 2020. The effect of the global warming and environmental temperature on the animal's molecular response and enzymatic activity. Journal of Analytical & Pharmaceutical Research. 9, 44–46. DOI: 10.15406/japlr.2020.09.00350.

Amiel, J.J., et al., 2017. The effects of incubation temperature on the development of the cortical forebrain in a lizard. Anim. Cogn. 20, 117-125. DOI 10.1007/s10071-016-0993-2.

Andrews, O., et al., 2018. Implications for workability and survivability in populations exposed to extreme heat under climate change: a modelling study. Lancet Planet Health. 2, 540-547. doi.org/10.1016/S2542-5196(18)30240-7.30240-7.

Beckers, L., et al., 2018. Neuronal dysfunction and behavioural abnormalities are evoked by neural cells and aggravated by inflammatory microglia in peroxisomal β-oxidation deficiency. Front. Cell. Neurosci. 12, 136. DOI: 10.3389/fncel.2018.00136.

Bouteloup, C., et al., 2009. Hypermetabolism in ALS patients: an early and persistent phenomenon. Journal of Neurology 256, 1236-1242. DOI: 10.1007/s00415-009-5100-z.

C3S (Copernicus Climate Change Service). 2020. European State of the Climate 2019, pp 10. Available from the European Union Copernicus project (https://climate.copernicus.eu/ ESOTC/2019).

Calabrese, V., et al., 2018. Aging and Parkinson's Disease: inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. Free Radic. Biol. Med. 115, 80-91. DOI: 10.1016/j.freeradbiomed.2017.10.379.

Campanella, C., et al., 2018. Heat shock proteins in Alzheimer's Disease: role and targeting. Int. J. Mol. Sci. 19, 2603. DOI: 10.3390/ijms19092603.

Carrettiero, D.C., et al., 2015. Temperature and toxic Tau in Alzheimer's disease: new insights. Temperature (Austin). 2, 491-498. DOI: 10.1080/23328940.2015.1096438.

Ceravolo, R., et al., 2013. Neuropathy and levodopa in Parkinson's disease: evidence from a multicenter study. Mov. Disord. 28, 1391-1397. DOI: 10.1002/mds.25585.

Chauderlier, A., et al., 2017. In vivo hyperthermic stress model: an easy tool to study the effects of oxidative stress on neuronal Tau functionality in mouse brain. Methods Mol. Biol. 1523, 369–373. DOI: 10.1007/978-1-4939-6598-4_25.

Chauhan, N.R., et al., 2017. Heat stress-induced neuroinflammation and aberration in monoamine levels in hypothalamus are associated with temperature dysregulation. Neuroscience. 358, 79-92. DOI:10.1016/j.neuroscience.2017.06.023.

Chen, H.L., et al., 2020. Alteration of brain temperature and systemic inflammation in Parkinson's disease. Neurol. Sci. 41, 1267-1276. DOI: 10.1007/s10072-019-04217-3.

Cheshire, W.P., 2016. Thermoregulatory disorders and illness related to heat and cold stress. Auton. Neurosci. 196, 91-104. DOI: 10.1016/j.autneu.2016.01.001.

Christoforidou, E., et al., 2020. Potential of activated microglia as a source of dysregulated extracellular microRNAs contributing to neurodegeneration in amyotrophic lateral sclerosis. J. Neuroinflammation. 17, 135. DOI: 10.1186/s12974-020-01822-4

Coon, E.A., et al., 2020 Sweating Disorders 26,116-137. doi: 10.1212/CON.0000000000000813.

Coogan, A.N., et al., 2013. The circadian system in Alzheimer's disease: disturbances, mechanisms, and opportunities. Biol. Psychiatry. 74, 333-339. doi.org/10.1016/j.biopsych.2012.11.021.

COP21 (2015): United Nations Framework Convention on Climate Change 'Paris Agreement', available from the UNFCCC web site: https://unfccc.int/process-and-meetings/the-paris-agreement/the-paris-agreement Cunnane, S.C., et al., 2011. Brain fuel metabolism, aging and Alzheimer's disease. Nutrition. 27, 3-20.

Cunnane, S.C., et al., 2011. Brain fuel metabolism, aging and Alzheimer's disease. Nutrition. 27, 3-20. DOI: 10.1016/j.nut.2010.07.021.

Dahl, G.E., et al., 2020. Heat stress impacts immune status in cows across the life cycle. Front. Vet. Sci. 7, 116. doi: 10.3389/fvets.2020.00116.

Dantzer, R., 2018. Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa Physiol Rev. 98: 477–504. doi.org/10.1152/physrev.00039.2016.

Dayananda, B., Webb, J.K., 2017. Incubation under climate warming affects learning ability and survival in hatchling lizards. Biol. Lett. 13, 20170002. DOI: 10.1098/rsbl.2017.0002.

Della Marta, P.M., et al., 2007. Doubled length of western European summer heat waves since 1880. J. Geophys. Res. 112, D15103. doi:10.1029/2007JD008510.

Dentel, C., et al., 2013. Degeneration of serotonergic neurons in amyotrophic lateral sclerosis: a link to spasticity. Brain. 136, 483-493 DOI: 10.1093/brain/aws274..

Doppler, K., et al., 2014. Cutaneous neuropathy in Parkinson's disease: a window into brain pathology. Acta Neuropathol. 128, 99-109. DOI: 10.1007/s00401-014-1284-0.

Dorsey, E.R., et al., 2018. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 17, 939-953. DOI: 10.1016/S1474-4422(18)30499-X.

Dukay, B., et al., 2019. Heat-shock proteins in neuroinflammation. Front. Pharmacol. 10, 920. doi: 10.3389/fphar.2019.00920.

Dupuis, L., et al., 2004. Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: benefit of a high-energy diet in a transgenic mouse model. Proc. Natl. Acad. Sci. USA. 101, 11159-11164. doi.org/10.1073/pnas.0402026101.

Ely, B.R., et al., 2015. Can targeting glutamate receptors with long-term heat acclimation improve outcomes following hypoxic injury? Temperature (Austin). 2, 51-52. DOI: 10.4161/23328940.2014.992657.

El-Orabi, N., et al., 2011. Heat-induced inhibition of superoxide dismutase and accumulation of reactive oxygen species leads to HT22 neuronal cell death. J. Therm. Biol. 36, 49-56. DOI: 10.1016/j.jtherbio.2010.11.002.

.El Oussini, H., et al., 2017. Degeneration of serotonin neurons triggers spasticity in amyotrophic lateral sclerosis. Ann. Neurol. 82, 444-456. DOI:10.1002/ana.25030.

Eschbach, J., et al., 2013. PGC-1alpha is a male-specific disease modifier of human and experimental amyotrophic lateral sclerosis. Hum. Mol. Genet. 22, 3477-3484. DOI: 10.1093/hmg/ddt202.

Feigin, V.L., et al., 2019. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18, 459-480. DOI: 10.1016/S1474-4422(18)30499-X.

Fragniere, A.M.C., et al., 2019. Hyperosmotic stress induces cell-dependent aggregation of α-synuclein. Sci. Rep. 9**,** 2288. DOI: 10.1038/s41598-018-38296-7.

Fukuoka, M., et al., 2014. Gene silencing mediated by endogenous microRNAs under heat stress conditions in mammalian cells. PLoS One, 9, e103130. DOI: 10.1371/journal.pone.0103130.

Ghavami, M., et al., 2013. Physiological Temperature Has a Crucial Role in Amyloid Beta in the Absence and Presence of Hydrophobic and Hydrophilic Nanoparticles. ACS Chem Neurosci. 4, 375-378. doi: 10.1021/cn300205g.

Gelders, G., et al., 2018. Linking neuroinflammation and neurodegeneration in Parkinson's Disease. J. Imm. Res. ID 4784268. DOI: 10.1155/2018/4784268.

Ginhoux, F., et al., 2013. Origin and differentiation of microglia. Front. Cell Neurosci. 7, 45. DOI: 10.3389/fncel.2013.00045.

Gorges, M., et al., 2017. Hypothalamic atrophy is related to body mass index and age at onset in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry. 88, 1033-1041. doi.org/10.1136/jnnp-2017-315795.

Gostimirovic, M., et al., 2020. The influence of climate change on human cardiovascular function. Arch Environ Occup Health. 75, 406-414. doi: 10.1080/19338244.2020.1742079.

Gulcebi, M.I., et al., 2021. Climate change and epilepsy: Insights from clinical and basic science studies. Epilepsy Behav. 116, 107791. doi: 10.1016/j.yebeh.2021.107791.

Habibi, L.,et al., 2014. Global warming and neurodegenerative disorders: speculations on their linkage Bioimpacts. 4, 167-170. doi: 10.15171/bi.2014.013.

Hermosura, M.C., et al., 2008. Altered functional properties of a TRPM2 variant in Guamanian ALS and PD. Proc. Natl. Acad. Sci. USA. 105, 18029-18034. DOI: 10.1073/pnas.0808218105.

Homma, T., Fujii, J., 2016. Heat stress promotes the down-regulation of IRE1α in cells: an atypical modulation of the UPR pathway. Exp. Cell Res. 349, 128-138. DOI: 10.1016/j.yexcr.2016.10.006.

Huisman, M.H.B., et al., 2015. Effect of presymptomatic body mass index and consumption of fat and alcohol on amyotrophic lateral sclerosis. JAMA Neurol. 72, 1155-1162. DOI: 10.1001/jamaneurol.2015.1584.

Hunt, A.P., et al., 2020. Could Heat Therapy Be an Effective Treatment for Alzheimer's and Parkinson's Diseases? A Narrative Review. Front Physiol. 10, 1556. doi: 10.3389/fphys.2019.01556.

Iodice, V., et al., 2011. Cardiovascular autonomic dysfunction in MSA and Parkinson's disease: similarities and differences. J. Neurol. Sci. 310, 133-138. DOI: 10.1016/j.jns.2011.07.014.

IPCC (Intergovernmental Panel on Climate Change), 2014, 5th Assessment Report, Synthesis Report, Summary for Policymakers. pp 31. Available from IPCC (https://www.ipcc.ch/report/ar5/syr/).

IPCC (Intergovernmental Panel on Climate Change), 2018, Special Report on "Global warming of 1.5° degrees - Summary for Policy Makers"; pp 25. Available from IPCC (https://www.ipcc.ch/site/assets/uploads/sites/2/2019/05/SR15_SPM_version_report_LR.pdf).

IPCC (Intergovernmental Panel on Climate Change), 2019, Special Report on 'Climate change and land'. pp 100. Available from IPCC (https://www.ipcc.ch/srccl/).

Jiang, Q., et al., 2013. Hyperthermia impaired human visual short-term memory: an fMRI study. Int. J. Hyperth. 29, 219–224. DOI: 10.3109/02656736.2013.786141.

Ji, T., et al., 2020. Does perturbation in the mitochondrial protein folding pave the way for neurodegeneration diseases? Ageing Res. Rev. 57, 100997. DOI: 10.1016/j.arr.2019.100997.

Jones, D.R, et al., 2014. Targeting heat shock proteins to modulate α-synuclein toxicity. Ther. Adv. Neurol. Disord. 7, 33-51. doi.org/10.1177/1756285613493469.

Kabir, M.F., et al., 2018. Endoplasmic Reticulum Stress and Autophagy. DOI: 10.5772/intechopen.81381.

Katschinski, D.M., 2004. On heat and cells and proteins. Physiology. 19, 11-15. doi.org/10.1152/nips.01403.2002.

Keil, G., et al., 2015. Being cool: how body temperature influences ageing and longevity. Biogerontology. 16, 383-397. DOI: 10.1007/s10522-015-9571-2.

Kempuraj, D., et al., 2016. Neuroinflammation induces neurodegeneration. J. Neurol. Neurosurg. Spine. 1, 1003.

Kim, J.A., Connors, B.W., 2012. High temperatures alter physiological properties of pyramidal cells and inhibitory interneurons in hippocampus. Front. Cell. Neurosci. 6, 27 DOI: 10.3389/fncel.2012.00027

Kim, D., et al., 2014. What is the clinical significance of cerebrospinal fluid biomarkers in Parkinson's disease? Is the significance diagnostic or prognostic? Exp. Neurobiol. 23, 352-364. doi: 10.5607/en.2014.23.4.352.

Kingsbury, A.E., et al., 2010. Brain stem pathology in Parkinson's disease: an evaluation of the Braak staging model. Mov. Disord. 25, 2508-2515. DOI: 10.1002/mds.23305.

Kiyatkin, E.A., 2019. Brain temperature and its role in physiology and pathophysiology: Lessons from 20 years of thermorecording Temperature (Austin). 6, 271–333. DOI: 10.1080/23328940.2019.1691896.

Knight, E.M., et al., 2013. Age-related changes in core body temperature and activity in triple-transgenic Alzheimer's disease (3xTgAD) mice. Dis. Model. Mech. 6, 160-170. DOI: 10.1242/dmm.010173.

Konovalova, J., et al., 2019. Interplay between microRNAs and oxidative stress in neurodegenerative diseases. Int. J. Mol. Sci. 20, 6055.

Laukkanen, T., Kunutsor, S., Kauhanen, J., Laukkanen, J.A., 2017. Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men. Age and Ageing. 46(2), 245-249. DOI: 10.1093/ageing/afw212.

Lee, W., et al., 2015. Heat stress-induced memory impairment is associated with neuroinflammation in mice. J. Neuroinflammation 12, 102 DOI: 10.1186/s12974-015-0324-6.

Leon, L.R., Helwig, B.G., 2010. Heat stroke: role of the systemic inflammatory response. J. Appl. Physiol. 109, 1980-1988 DOI: 10.1152/japplphysiol.00301.2010.

Li, L., et al., 2015. Heat stress induces apoptosis through a Ca^{2+}-mediated mitochondrial apoptotic pathway in human umbilical vein endothelial cells. PLoS One 9, e111083 DOI: 10.1152/japplphysiol.00301.2010.

Lim, K.H., 2019. Diverse misfolded conformational strains and cross-seeding of misfolded proteins implicated in neurodegenerative diseases. Front. Mol. Neurosci. 12, 158 doi: 10.3389/fnmol.2019.00158.

Linares, C., et al., 2017. Short-term association between environmental factors and hospital admissions due to dementia in Madrid. Environ Res. 152, 214-220. doi: 10.1016/j.envres.2016.10.020.

Liu, G., et al., 2012$_b$. α-synuclein, LRRK2 and their interplay in Parkinson's disease. Future Neurol. 7, 145-153 DOI: 10.2217/fnl.12.2.

Liu, T., et al., 2017. NF-κB signaling in inflammation. Signal Transduct. Target. Ther. 2, 17023 DOI: 10.1038/sigtrans.2017.23.

Liu, Y., et al., 2012$_a$. Heat stress activates ER stress signals which suppress the heat shock response, an effect occurring preferentially in the cortex in rats. Mol. Biol. Rep. 39, 3987–3993.

Logroscino, G., et al., 2018. Global, regional, and national burden of motor neuron diseases, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 17, 1083-1097.

Lu, S.H., et al., 2010. A systematic review of body temperature variations in older people. J. Clin. Nurs. 19, 4-16 doi.org/10.1111/j.1365-2702.2009.02945. x.

Malyshev, I., 2013. The Role of HSP70 in the Protection of: (A) The Brain in Alzheimer's Disease and (B) The Heart in Cardiac Surgery. Immunity, Tumors and Aging: The Role of HSP70. Springer. 6, 113-139 doi.org/10.1111/j.1365-2702.2009.02945. x.

Mecocci, P, et al., 2018. Brain Aging and Late-Onset Alzheimer's Disease: A Matter of Increased Amyloid or Reduced Energy? Review J Alzheimers Dis. 64, S397-S404. doi: 10.3233/JAD-179903.

Medinas, D.B., et al., 2019. ER stress links aging to sporadic ALS. Aging. 11, 5-6 DOI: 10.18632/aging.101705.

Michaelson, N., et al., 2017. Cytokine expression levels in ALS: a potential link between inflammation and BMAA-triggered protein misfolding. Cytokine Growth Factor Rev. 37, 81-88 DOI: 10.1016/j.cytogfr.2017.05.001.

Miller, D.J., Fort, P.E., 2018. Heat shock proteins regulatory role in neurodevelopment. Front. Neurosci. 12, 821 DOI: 10.3389/fnins.2018.00821.

Mujahid, A., et al., 2007. Mitochondrial oxidative damage in chicken skeletal muscle induced by acute heat stress. J Poult Sci. 44,439–44, doi.org/10.2141/jpsa.44.4395.

Neal, M, Richardson, J.R., 2018. Epigenetic regulation of astrocyte function in neuroinflammation and neurodegeneration. Biochim. Biophys. Acta Mol. Basis Dis. 1864, 432-443. DOI: 10.1016/j.bbadis.2017.11.004

Nichols, E., et al., 2019. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18, 88-106, doi.org/10.1016/S1474-4422(18)30403-4.

O'Donnell, S., 2018. The neurobiology of climate change. Naturwissenschaften. 105, 11 DOI: 10.1007/s00114-017-1538-5.

Orimo, S., et al., 2008. Axonal alpha-synuclein aggregates herald centripetal degeneration of cardiac sympathetic nerve in Parkinson's disease. Brain 131, 642-650 DOI: 10.1093/brain/awm302.

Pallotta, M.M., et al., 2017. Brain gene expression is influenced by incubation temperature during Leopard Gecko (Eublepharis macularius) development. J. Exp. Zool. B Mol. Dev. Evol. 328, 360-370 DOI: 10.1002/jez.b.22736.

Pasquinelli, A., et al., 2016. Gly482Ser PGC-1□ gene polymorphism and exercise-related oxidative stress in amyotrophic lateral sclerosis patients. Front. Cell. Neurosci. 10, 102 DOI: 10.3389/fncel.2016.00102.

Peinkhofer, C., et al., 2020. Global Warming and Neurological Practice: Systematic Review. MedRxiv. doi: org/10.1101/2020.12.18.20248515 doi.org/10.1101/2020.12.18.20248515.

Planel, E., et al., 2004. Alterations in glucose metabolism induce hypothermia leading to tau hyperphosphorylation through differential inhibition of kinase and phosphatase activities: implications for Alzheimer's disease. J. Neurosci. 24, 2401-2411 DOI: 10.1523/JNEUROSCI.5561-03.2004.

Podgorny, P.J., et al., 2016. Evidence for small fiber neuropathy in early Parkinson's disease. Parkinsonism. Relat. Disord. 28, 94-99 DOI: 10.1016/j.parkreldis.2016.04.033.

Power, J.H.T., et al., 2017. Lewy Bodies and the mechanisms of neuronal cell death in Parkinson's Disease and Dementia with Lewy Bodies. Brain Pathol. 27, 3-12 doi.org/10.1111/bpa.12344.

Qu, L., et al., 2007. Hyperthermia decreases GABAergic synaptic transmission in hippocampal neurons of immature rats. Neurobiol. Dis. 27, 320-327 doi.org/10.1016/j.nbd.2007.06.003.

Qu, Z., et al., 2018. Neuroprotection by Heat Shock Factor-1 (HSF1) and Trimerization-Deficient Mutant Identifies Novel Alterations in Gene Expression. Sci Rep. 8, 17255 DOI: 10.1038/s41598-018-35610-1.

Rango, M., et al., 2014. The brain is hypothermic in patients with mitochondrial diseases. J. Cereb. Blood Flow Metab. 34, 915-920 doi.org/10.1038/jcbfm.2014.38.

Reish, H.E.A., Standaert, D.G., 2015. Role of α-synuclein in inducing innate and adaptive immunity in Parkinson disease. J. Parkinson Dis. 5, 1-19 doi: 10.3233/JPD-140491.

Ruszkiewicz, J.A., et al., 2019. Brain diseases in changing climate. Environ. Res. 177, 108637 DOI: 10.1016/j.envres.2019.108637.

Salminen, A., et al., 2020. Stress activates immunosuppressive network: implications for aging and Alzheimer's disease. J. Mol. Med. 98, 633-650doi: 10.1007/s00109-020-01904-z.

Schaer, C., Jendritzky, G., 2004. Hot news from summer. Nature. 432, 559-560 DOI: 10.1038/432559a.

Scheltens, P., et al., 2016. Alzheimer's disease. Lancet. 388, 505-517. doi: 10.1016/S0140-6736(15)01124-1.

Seminary, E.R., et al., 2018. Modeling protein aggregation and the heat shock response in ALS iPSC-derived motor neurons. Front. Neurosci. 12, 86 doi: 10.3389/fnins.2018.00086.

Sharma, H.S., 2006. Hyperthermia influences excitatory and inhibitory amino acid neurotransmitters in the central nervous system. An experimental study in the rat using behavioural, biochemical, pharmacological, and morphological approaches. J. Neural Transm. 113, 497-519DOI: 10.1007/s00702-005-0406-1.

Sharma, H.S., Hoopes P.J., 2009. Hyperthermia induced pathophysiology of the central nervous system Int. J. Hypertherm. 19, 325-54. doi: 10.1080/0265673021000054621.

Sharma, H.S., et al., 2010. Cerebrolysin reduces blood-cerebrospinal fluid barrier permeability change, brain pathology, and functional deficits following traumatic brain injury in the rat. Ann. N. Y. Acad. Sci. 1199, 125–137 DOI: 10.1111/j.1749-6632.2009.05329. x.

Shi, L., et al., 2015. Impacts of temperature and its variability on mortality in New England. Nat. Clim. Chang. 5, 988-991 DOI: 10.1038/nclimate2704.

Shi, L., et al., 2016. Chronic effects of temperature on mortality in the Southeastern USA using satellite-based exposure metrics. Sci. Rep. 6, 30161 DOI: 10.1038/srep30161.

Singh, I.S., et al., 2013. Fever, hyperthermia and the heat shock response. Int J Hyperthermia. 29, 423-35. doi: 10.3109/02656736.2013.808766.

Sinigaglia-Coimbra, R., et al., 2002. Postischemic hypertermia induces Alzheimer-like pathology in the rat brain. Acta Neuropathol. 103, 444–452 DOI: 10.1007/s00401-001-0487-3.

Slimen, I.B., et al., 2014. Reactive oxygen species, heat stress and oxidative-induced mitochondrial damage. A Rev. Int. J. Hyperth. 30, 513–523 DOI: 10.3109/02656736.2014.971446.

Song, K., et al., 2016. The TRPM2 channel is a hypothalamic heat sensor that limits fever and can drive hypothermia. Science 353, 1393-1398. DOI: 10.1126/science. aaf7537.

Stephenson, J., et al., 2018. Inflammation in CNS neurodegenerative diseases. Immunology. 154, 204-219 doi.org/10.1111/imm.12922.

Stott, P. A., et al., 200. Human contributions to the European heatwave of 2003. Nature. 432, 610-614 DOI: 10.1038/nature03089.

Sun, G., et al., 2013. Hyperthermia-induced disruption of functional connectivity in the human brain network. PLoS One 8, e61157. DOI: 10.1371/journal.pone.0061157.

Suzuki, K., et al., 2020. Characterization and modulation of systemic inflammatory response to exhaustive exercise in relation to oxidative stress. Antioxidants. 9, 401.

Sweeney, P., et al., 2017. Protein misfolding in neurodegenerative diseases: implications and strategies Transl Neurodegener. 2017; 6. doi: 10.1186/s40035-017-0077-5

Tan, C.C.S., et al., Thermoregulation in the Aging Population and Practical Strategies to Overcome a Warmer Tomorrow. Proteomics 2020, 20, 1800468. https://doi.org/10.1002/pmic.201800468

Thornton, C, et al., 2017. Oxidative stress and endoplasmic reticulum (ER) stress in the development of neonatal hypoxic-ischaemic brain injury. *Biochem. Soc. Trans.* 45, 1067-1076 DOI: 10.1042/BST20170017.

Titus, D.J., et al., 2015. Emergence of cognitive deficits after mild traumatic brain injury due to hyperthermia. Exp. Neurol. 263, 254–262 DOI: 10.1016/j.expneurol.2014.10.020.

UKMO (United Kingdom Met. Office), 2003. The heatwave of 2003 in U.K. Met Office report (available at https://www.metoffice.gov.uk/weather/learn-about/weather/case-studies/heatwave).

Vabulas, R. M, et al., 2010. Protein Folding in the Cytoplasm and the Heat Shock Response Cold Spring Harb Perspect Biol. 2, a004390. doi: 10.1101/cshperspect. a004390.

Valdinocci, D., et al., 2017. Potential modes of intercellular α-synuclein transmission. Int. J. Mol. Sci. 18, 469 doi: 10.3390/ijms18020469.

Vandal, M., et al., 2016. Impaired thermoregulation and beneficial effects of thermoneutrality in the 3×Tg-AD model of Alzheimer's disease. Neurobiol Aging. 43, 47-57 DOI: 10.1016/j.neurobiolaging.2016.03.024.

Vercruysse, P., et al., 2016. Alterations in the hypothalamic melanocortin pathway in amyotrophic lateral sclerosis. Brain. 139, 1106-1122 DOI: 10.1093/brain/aww004.

Waalen, J., Buxbaum, J.N., 2011. Is older colder or colder older? The association of age with body temperature in 18,630 individuals. J. Gerontol. A Biol. Sci. Med. Sci. 66, 487-492 doi.org/10.1093/gerona/glr001.

Wang, Z., et al., 2013. The role of mitochondria- derived reactive oxygen species in hyperthermia- induced platelet apoptosis. PLOS One. 8, e75044 10.1371/journal.pone.0075044.

Webers, A., et al., 2020. The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease. Immunol. Cell Biol. 98, 28-41 DOI: 10.1111/imcb.12301.

Wei, Y., et al., 2019. Associations between seasonal temperature and dementia-associated hospitalizations in New England. Environ. Int. 126, 228-233 DOI: 10.1016/j.envint.2018.12.054.

White, M.G., et al., 2012. Mitochondrial dysfunction induced by heat stress in cultured rat CNS neurons. J. Neurophysiol. 108, 2203-2214 DOI: 10.1152/jn.00638.2011.

Whittington, R.A., et al., 2010. Hypothermia and Alzheimer's disease neuropathogenic pathways. Curr. Alzheimer Res. 7, 717-725 DOI: 10.2174/156720510793611646.

WHO Guidance for Climate Resilient and Environmentally Sustainable Health Care Facilities 12 October 2020.

WMO, 2021: The state of the global climate in 2020. World Meteorological Organization, accessible from the WMO web site: https://public.wmo.int/en/our-mandate/climate/wmo-statement-state-of-global-climate.

Yan, D.Y. and Xu, B., 2020. The Role of Autophagy in Manganese-Induced Neurotoxicity. Front. Neurosci. 14, 574750 DOI: 10.3389/fnins.2020.574750.

Yu, T. et al., 2015. Morphological control of mitochondrial bioenergetics. Frontiers in Bioscience, 20, 229-246 DOI: 10.2741/4306.

Zanobetti, A., et al., 2012. Summer temperature variability and long-term survival among elderly people with chronic disease. Proc. Natl. Acad. Sci. USA. 109, 6608-6613 doi: 10.1073/pnas.1113070109.

Zanobetti, et al., 2013. Susceptibility to mortality in weather extremes: effect modification by personal and small-area characteristics. Epidemiology 2013;24:809-819 doi: 10.1097/01.ede.0000434432.06765.91.

Zhao, D., et al., 2017. Impact of short-term temperature variability on emergency hospital admissions for schizophrenia stratified by season of birth. Int J Biometeorol. 61, 589-599. doi: 10.1007/s00484-016-1235-7.

Zlotnik, A., et al., 2010. The effect of hyperthermia on blood glutamate levels. Anesth. Analg. 111 1497-1504 doi: 10.1213/ANE.0b013e3181fc0112.

Zorov, D. B., et al., 2014. Mitochondrial reactive oxygen species (ROS) and ROS- induced ROS release. Physiol Rev. 94, 909-950 /doi.org/10.1152/physrev.00026.2013.

Legends

Figure 1 Scheme of the main heat-affected pathways in brain cells.

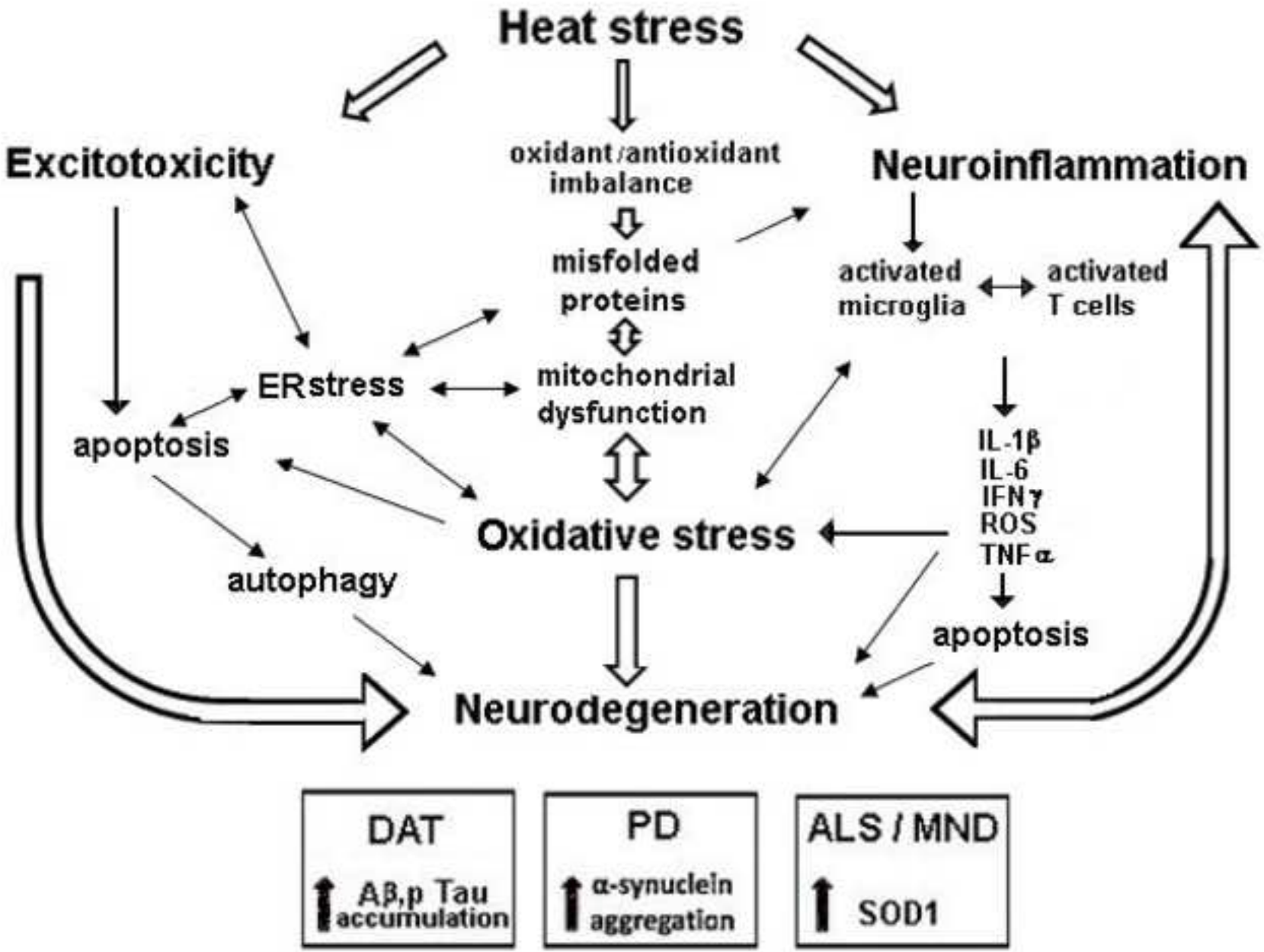
Table 1. Glossary of terms, definitions of commonly used terms relating to heat conditions.

Heat wave	A period of 3 or more consecutive days during which the air temperature exceeds the average maximum temperature by 5 °C.
Heat stress	Perceived discomfort and physiological strain caused by exposure to a hot environment, especially during physical work.
Heat stroke	Severe condition marked by a core temperature > 40°C and central nervous system abnormalities such as delirium, convulsions, or coma resulting from exposure to environmental heat (*classic heat stroke*) or strenuous physical exercise (*exertional heat stroke*).
Heat exhaustion	Mild-to-moderate illness that can occur after exposure to high temperature, aggravated by water or salt deficiency; signs and symptoms include weakness, fatigue and discomfort with intense thirst; core temperature may be normal, below normal, or slightly elevated (> 37°C, but < 40°C).
Hyperthermia	A rise in body temperature above the hypothalamic set point when heat-dissipating mechanisms are impaired (by drugs or disease) or overwhelmed by external (environmental or induced) or internal (metabolic) heat.
Multiorgan-dysfunction syndrome	Continuum of changes that occur in more than one organ system after an insult such as trauma, sepsis, or heat stroke.

Table 2. Summary of the reported pathophysiologic mechanisms of heat stress toward neurodegeneration.

Diseases	**Pathophysiologic mechanisms**	*Key references*
Neurodegenerative disease	Enhanced oxidative stress and neuroinflammation leading to increased neurodegeneration	Reish et al., 2015, Michaelson et al., 2017, Webers et al., 2020
DAT	Aβ expression upregulation and phosphorylated Tau deposition HSP-60 loss of function	Campanella et al., 2018
PD	α–syn expression dysregulation	Fragniere et al., 2019
MND	Increased levels of phosphorylated HSF-1	Qu et al., 2018

Figure 1



Declaration of competing interest:

The Authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of competing financial interest:

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.